REMARKS

THE INVENTION:

This invention is a novel means for selectively controlling the expression of a target protein in a cell. The invention involves the binding of a sequence-specific oligonucleotide to a subsequence of the target protein mRNA where the subsequence is limited to the coding sequences of the mRNA.

As previously explained, this invention reflects thinking which was in direct conflict with the conventional wisdom of the time. Although others were discussing the possibility of using mRNA as targets for control of expression using complementary oligonucleotides, the conventional thinking was limited to oligonucleotides that hybridized to accessible regions of the mRNA, such regions were limited to the ribosomal binding regions and tRNA binding regions. The conventional wisdom clearly suggested avoiding the coding regions of mRNA due to concerns of secondary structure. The attached declarations of Drs. Dennis Schwartz and Jerry Ruth provide interpretation and evidence of the state of the art in 1981.

THE STATUS OF THE CLAIMS:

Claims 64-72 are pending. The claims stand rejected under 35 U.S.C. §112, first paragraph and 35 U.S.C. §103.

35 U.S.C. §112, FIRST PARAGRAPH:

Claims 64-72 are rejected under §112, first paragraph. The Examiner states that the disclosure is only enabling for claims limited to stabilized forms of oligodeoxyribonucleotides that are phosphotriesters. The Examiner cites to MPEP §§706.03(n) and (z). In addition, the Examiner refers to a previous office action mailed on April 1, 1992, citing the third full paragraph of page 2. This paragraph states that

> [the] instant application does not give one of skill in the art the guidance in connection with other forms of oligodeoxyribonucleotides that would be stable *in vivo*. In the absence of such a teaching it

would require undue experimentation for one of skill to discover and synthesize such compounds.

The Examiner proceeds to comment at length on the inadequacy of using references published after the priority date for overcoming a §112 rejection. Applicant no longer relies on those references.

Finally the Examiner notes correctly that the pending claims encompass both oligodeoxyribo- and oligoribonucleotides. He urges that the instant application does not teach one of skill how to make or use oligo**ribo**nucleotides and that there is no data and no methods for getting short DNAs or RNAs into cells

Applicant urges that the Examiner's primary reasoning is misplaced. The central issue of an enablement rejection is undue experimentation. Would it require undue experimentation to carry out the invention as claimed? The Examiner does not urge that the invention would not work; but that it would require undue experimentation to identify alternative nucleotide analogues that would work. Applicant advances that this reasoning is misplaced because it is irrelevant to the invention of the pending claims. This invention is not the discovery of novel stabilized nucleotide analogues. It is the discovery that oligonucleotides of greater than 14 bases can effectively bind to the coding region of a mRNA and inhibit translation. The selection of a stabilized oligonucleotide is preferred but is not required and is not a point of patentability.

The Examiner is reminded that the pending claims are method claims using nucleic acid, and not composition claims to novel nucleic acid analogues. There is clear decisional law that enablement issues for such claims must be confined to the patentable or "inventive principles" of the claimed method. The fact that improvements or novel compounds might be developed at a later time and used in the claimed method does not bar the patenting of the method covering those improvements or compounds.

The three seminal cases setting forth this critical point of law are *Application of Fuetterer*, 319 F.2d 259, 138 USPQ 217 (CCPA 1963); *Application*

of Herschler, 591 F.2d 693, 200 USPQ 711 (CCPA 1979) and *In re Lange*, 209 USPQ 288 (CCPA 1981). In *Fuetterer*, the applicant had discovered that the addition of a protein with an inorganic salt to the materials used to make tire tread increased the stopping ability of tires made from the materials. The CCPA reversed the rejections of the Patent Office. Amongst the various rejections was a breadth rejection. The breadth rejection was analogous to our pending rejection under §112. The examiner in *Fuetterer* argued that the scope of the claim was too broad and the amount of experimentation required to successfully use undisclosed inorganic salts should require the applicant to restrict his claims to the disclosed salts. In reversing the rejection, the CCPA explained that this invention was the combination of inorganic salts with the other elements of the claim. The fact that novel inorganic salts might be later developed should not preclude broad claims to the combination. To hold otherwise would be to place an impossible burden on the applicant to test thousands of compounds, both known and unknown, in order to obtain practical protection for his invention.

Herschler followed *Fuetterer*. In *Herschler*, the applicants had discovered that dimethylsulfoxide (DMSO) was useful as a transdermal carrier for steroidal agents. In reversing an array of rejections, which by necessity included a finding that the priority application describing a single steroid supported a claim to the genus of all steroids, the Court affirmed its decision in *Fuetterer*. The CCPA explained that *Herschler*'s claims were not drawn to novel steroids, and that so long as the class could be expected to be carried across the skin by DMSO the claim could encompass any steroid, known or unknown. As in *Fuetterer*, the CCPA reminded the Patent Office that the inventive principle was directed to a method of administration of steroids and that the steroids were not the point of patentability.

Lange harmonizes with *Herschler* and *Fuetterer* but does not rely on these two earlier cases. In *Lange* the appellant had claimed electrical devices that were physically coated with electronegative gases to inhibit electric arcs (sparks). There was a §112 rejection raised because the grandparent application did not teach how to craft entire electrodes incorporating these gases but did teach how

to superimpose the gases on the surfaces of electrodes. The CCPA reversed the rejection because the inventive principle did not reside in the preparation of electrodes but in the use of the electronegative gases to prevent arcing. The court understood that there might be new inventions involving means for crafting electrodes using the gases but this would not preclude claims that dominated these subsequent inventions. The court states:

> ...although appellant can be required to limit his claims to that subject matter which is adequately disclosed, the existence of species which are not adequately disclosed does not require that the entire application be found nonenabling...[cites omitted]. This is especially true in this case where, as stated by appellant at oral argument, the method of forming the electrodes is not the inventive principle.

Claims 64-71 are not directed to novel forms of stabilized nucleic acid. Stabilized nucleic acid is not the inventive principle of this invention. Stabilized is a preferred inhibitor but it is not the only inhibitor of protein expression. Although the application indicates a preference for thiol analogs of nucleic acid, any nucleic acid will work. The literature is filled with reports of various nucleic acid analogs used to inhibit cellular processes. For example, Miller (1977) describes neutral, nonionic nucleic acids; Befort (1974) used methylated ribonucleic acid; and, Summerton (1979) describes a number of early reports using various nucleic acid analogs to inhibit viral infections (Summerton at page 89).

Applicant respectfully requests that the Examiner focus his attention on the inventive principle in the pending claims. This principle is the discovery that one can inhibit specific protein expression if you target the coding region of a mRNA with a nucleic acid of greater than about 14 nucleotides. It is irrelevant whether the nucleic acid is RNA, DNA, a synthetic nucleic acid analog, or DNA encapsulated in a liposome or a viral capsid as described by Summerton (1979) at pages 93-94. These are all separate areas for later research that may represent independently patentable improvements over this invention; but, the possibility of subsequent inventions should not preclude the pending claims from issuing because they are unrelated to the inventive principle.

The Examiner argues that there is no teaching of how to make or use ribonucleotides. Applicant responds that this is a trivial matter and that they need not teach what is already known in the art. The Examiner is already aware that RNA synthesis was readily available in 1981. This fact is evidenced by his citation of the Miller reference teaching the synthesis of ribonucleic acid analogs. Furthermore, as discussed in the accompanying §1.132 Declaration by Drs. Jerry Ruth and Dennis Schwartz, both chemical and enzymatic methods for oligoribonucleotide synthesis were well known in 1981. For example, by 1980 Ohtsuka and his colleagues had reported the synthesis by phosphodiester and phosphotriester methods of nine oligoribonucleotides corresponding to regions of an *Escherichia coli* tRNA, as well as ligation of some of these fragments to form an entirely synthetic tRNA (Nuc. Acids. Res. Symp. Series No. 7 (NARS), pp. 335-343 (1980), and cites therein). Equally illustrative of the state of the art in 1981 is a comment by Gumport *et al.*, who, in a 1980 paper on T4 RNA ligase, wrote "...the enzyme is now widely used to synthesize defined sequences of RNA." (NARS No. 7 (1980) p.p. 167-171 at 167; this paper and Ohtsuka *et al.* are offered as exhibits in the accompanying declaration). If the Examiner is aware of facts to the contrary regarding the synthesis of RNA in 1981, he should set them forth with particularity and support his reasons with references or an affidavit.

Finally, the Examiner raises the issue of cell uptake of nucleic acid. He comments that there are no data and methods for actually "getting short DNAs or RNAs into cells." As explained by the declarants, cells are quite amenable to internalizing short nucleic acid and nucleic acid analogs. There is nothing to teach. Normal cells naturally internalize these compounds. In fact the very literature relied upon by the Examiner to support his obviousness rejection teaches this fundamental fact. For example the Miller reference involves the effect of a trinucleotide analogue on mammalian cells and the Summerton reference discloses at pages 93-94 the routine uptake by animal cells of both RNA and DNA. At page 93, Summerton refers to a paper by Zamecnik and Stephenson (1978). This paper is already of record and applicant would like the Examiner to note that the authors acknowledge in the their paper that the DNA used in the study was analyzed by

Dr. Dennis Schwartz, whose Rule 132 declaration is before the Examiner. If the Examiner is aware of facts to the contrary regarding the nature of cellular uptake of nucleic acid he should set them forth with particularity and support his reasons with references or an affidavit.

Prior to addressing the obviousness rejection, applicant would ask the Examiner to reconsider his rejection under §112 in view of the MPEP §§706.3 (n) and (z). These sections of the MPEP are not applicable to a breadth rejection as articulated by the Examiner. These sections relate, respectively, to a technical requirement of the claims and to new matter rejections. Applicants are concerned that the Examiner has either miscited these sections or has raised a rejection that is not clearly set forth.

MPEP §706.03(n) requires correspondence between the scope of the claims and the disclosure presented to support the claims. The MPEP expressly states that the applicant should correct this defect by merely adding the corresponding language into the specification. It is not a fatal problem.

MPEP §706.03(n) is not applicable to the subject application because the original application had supporting language in the specification for each word of the pending claims. Nothing more is required and the Examiner's maintenance of the §112 rejection under this MPEP section is unclear. If the Examiner maintains his rejection over §706.03(n), applicant requests that he make specific reference to the offending language of the claims so that an appropriate amendment to the claims may be made.

The rejection in view of MPEP §706.03(z) acknowledges law that precludes a single example from supporting a broad genus where the invention is in an art that is unpredictable. The Examiner appears to have confused this new matter requirement with a utility-type rejection. The fact that 706.03(z) relates to new matter is clear when one views the facts of the two cited cases *In re Söll*, 97 F.2d 623 (CCPP 1938) and *In re Dreshfield*, 110 F.2d 234 (CCPP 1940).

The Examiner should be aware that these two cases involve amended claims which were not adequately supported by the original specification (which would include the original claims). Although the cases may not expressly state

that the appealed claims are amended claims, if the original claims had described the appealed embodiment, the issue would never had been raised by the Patent Office.

In *Söll*, the applicant was attempting to copy claims for an interference with a third party's patent. The invention involved injecting rubber with a hydrohalide (e.g., HCl, HBr, HI or HF). The application as originally filed disclosed only HF and the applicant unsuccessfully argued that the disclosure of the one species would immediately suggest to those of skill the broader group of halogens. *Söll* does not involve utility rejections. The claims were rejected because there was no support for the amended claims in the originally filed application. Had there been a description of other halogens, the new claims would have had the necessary support. This is not the situation in the instant application. The original claims were a part of the original specification and were also fully supported by the disclosure.

Dreshfield is on point with *Söll*. In *Dreshfield*, the applicant had invented an improved rosin size. A size is gelatinous filler for the pores in paper. The improvement was for the addition of an anti-oxidant to the rosin. The first part of the opinion, discussing claims 4 and 8, is not relevant to our situation. Those two claims recited anti-oxidants in general and were rejected for lack of invention (as obvious). Although the Patent Office had rejected these claims for undue breadth as well as for obviousness, the CCPA only spoke to the issue of inventiveness.

In contrast, claims 15-16 of the Dreshfield application related to specific chemical species of anti-oxidant and are relevant to the issue of MPEP §706.03(z). As originally filed, the specification disclosed only diaryl amines. The new claims on appeal claimed monoaryl and diaryl substituted amines as well as compounds with an amine and the aryl substituents attached to a non-amine constituent. These claims were rejected as articulated by the MPEP §706.03(z). To support a later amendment to claim a genus of compounds, the originally filed specification must enumerate sufficient numbers of the group or by other appropriate language indicate that the genus now being claimed is capable of

accomplishing the results desired. In other words, unlike in mechanical cases where a claim may be added to cover obvious variations on a theme not expressly described, different chemical compounds are not obvious variations on a theme and thus express support in the original application is required.

In the subject application, the specification as filed articulates the use of nucleic acid to inhibit expression of protein. There is nothing being added to the pending claims which did not appear in the originally filed specification. In view of the above remarks and the obvious inapplicability of the two MPEP sections, the applicants expect that the rejection under §112, first paragraph, will now be withdrawn.

35 U.S.C. §103.

The Examiner has rejected claims 64-72 under §103 as unpatentable over Itakura *et al.*, in view of Paterson *et al.* or Hastie *et al.* in further view of Summerton *et al.* or Miller *et al.*

Itakura is relied upon for disclosing means to synthesize oligonucleotides.

Secondary references of Patterson and Hastie teach hybrid arrested translation.

Tertiary references, Summerton and Miller, were relied upon for disclosing uptake of oligonucleotides by cells. Miller is further cited for teaching nonspecific inhibition of cellular protein synthesis by binding oligoribonucleotides to cellular mRNA and for suggesting that increased length would result in increased specificity.

Applicant has previously submitted an extensive argument in support of patentability and appreciates the Examiner's detailed consideration of the points set forth in the argument. Two Rule 132 declarations are submitted herewith in support of the scientific facts and interpretations of the references that underpin the arguments.

In brief, applicant's argument regarding non-obviousness focuses on the failure of the prior art to provide a reasonable expectation of success for a

process of arresting translation using oligonucleotides specific to the coding region of an mRNA. Applicant previously provided six objective reasons which included:

1. The conventional wisdom in 1981 regarded mRNA as having such extensive secondary structure and this structure would prevent an oligonucleotide complementary to the coding region from binding to the mRNA and arresting its translation.

2. The short probes of Miller (1977) were simply too short to effectively arrest translation even if they could bind to the mRNA. According to the declarants, the ribosomes which naturally untangle the secondary structure of mRNA would be expected to physically caste aside the probes during protein synthesis.

3. The Miller reference fails to specify the mRNA coding region as a possible binding target and fails to teach the appropriate length probes needed to arrest translation when the probes are bound to the coding regions of mRNA. Because the rejection relies upon the applicant's disclosure of the mRNA coding region as the specific target, the Examiner's rejection is built on hindsight reconstruction using the teachings of the applicant.

4. The Examiner's interpretation of Miller as suggesting longer oligonucleotides to achieve "greater specificity" is an interpretation that uses the applicant's disclosure as a guide to provide a patent defeating interpretation. Miller suggests using longer oligonucleotides to provide "greater specificity" but according to both declarants the "greater specificity" referred to by Miller was not a suggestion to target the mRNA coding region but to target the initiation regions of mRNA or amino acid acylation sites of tRNA where there was little secondary structure to block binding. As further explained by declarants, Dr. Miller's trimers would statistically bind to at least one triplet appearing every 64 bases. Any increase in oligomer length achieves "greater specificity" in a general sense. To view this statement as a suggestion to use longer oligonucleotides targeted to the coding region of mRNA is a clear application of hindsight. According to the declarants, the Examiner's interpretation of Miller goes well beyond its true intent.

5. The arrest of mRNA-directed protein expression by oligonucleotides *in vivo* is not predictable from the prior art teachings and there were multiple reasons provided explaining why the arrest of *in vivo* translation would be unpredictable and surprising. The declarants provide seven distinct and objective reasons in support of their position that one of skill would not have had a reasonable expectation that the use of a oligonucleotide complementary to a coding region of an mRNA would inhibit translation of the mRNA under *in vivo* conditions. The Examiner is required to rebut these arguments. For his convenience, applicant presents the seven objective reasons: (1) that the intact mRNA might not be physically accessible to complementary oligonucleotides due to proteins blocking the coding region; (2) that secondary structure of mRNA might block complementary oligonucleotide binding; (3) that short oligonucleotides might not have sufficient binding strength to block a ribosome designed to untangling internal duplexes in mRNA; (4) that the use of unsuitably long complementary oligonucleotides would have their own secondary structure that would interfere with hybridization of mRNA; (5) that polyamines might interfere with binding between oligonucleotides; (6) that the presence of excessive amounts of cation binding nucleic acid necessary to inhibit translation could very well affect the electropotential of the target cells and be toxic; and (7) that the majority of mRNA are not actually translated by cells but rapidly turned over thus presenting a logistical problem for this technology.

6. Finally it was explained that claims 66-68 recite precise lengths for the oligonucleotides. The lengths are elements that are not taught by the prior art and, at the shorter lengths, are critical to the operability of the invention.

In response to the multifaceted argument in the Preliminary Amendment, the Examiner advanced three rebuttal arguments. The Examiner first noted that some of the references relied upon to support the unexpected results were published after the priority filing date of this application. The Examiner urges that it was not proper to support a position of nonobviousness with publications that are not prior art. He then urged that nothing in the applicant's arguments rebuts the results reported in the secondary references of Patterson and Hastie.

Finally the Examiner relies on Summerton disclosing oligonucleotides that crosslink to and inactivate target sequences, and notes that none of the applicant's arguments address crosslinking.

Each of the three rebuttal arguments are addressed below.

A. RELIANCE ON REFERENCES PUBLISHED AFTER THE FILING DATE OF A PATENT APPLICATION IS NOT PROHIBITED IF LIMITED FOR PURPOSES OF ESTABLISHING NON-OBVIOUSNESS.

Applicant notes that the decisional law does not preclude use of subsequently published references to establish the state of the art at the time the application was filed. This law is in stark contrast to the use of such references to establish enablement. In fact, the Patent Office is the primary proponent of this point of law. In a number of written court opinions the CCPA affirmed the Patent Office's use of references published after the filing date of patent applications to define the state of the art at the time of filing the rejected application. The law is quite consistent on this point. It is entirely proper for either the Patent Office or an applicant to rely on subsequently published references to establish the intent of prior art or the state of art at the time of invention. For example in *In re Wilson*, 135 USPQ 442 (CCPA 1962), the court was asked to rule on the propriety of using a non-prior art publication stating a point of fact regarding polyurethane foam described in the prior art. The court stated: As evidence of the characteristics of prior art foam products, however, we know of no reason in law why it is not acceptable." The CCPA referred to this point of law as the "principle of *Wilson*." *In re Langer*, 183 USPQ 288 (1974). More recently, the Federal Circuit in *Ex parte Raychem Corp.*, 17 USPQ 2d 1417, 1420 (1990) following the law of *Wilson*, ruled that subsequently published materials can be relied upon as "relevant evidence as to the knowledge of those of ordinary skill in the art in the relevant time frame." The applicant's reliance on subsequently published references is fully within the *Wilson* principle. Dr. Tullis is merely establishing the factual and historical context of the references being cited against him. This strategy is entirely proper and has been long accepted as proper by the CCPA and the Federal Circuit.

In view of these opinions, applicant respectfully requests that the Examiner reconsider his decision to ignore the teachings of references that were offered to establish the unpredictability of the art at the time the application was filed. If the Examiner can cite to authority authorizing him to ignore these rebuttal references, he is respectfully asked to provide that authority.

Notwithstanding the above remarks, applicant notes that several of the references relied upon to establish the unpredictable nature of the art and to evidence the reasons why one of skill would not have expected success using oligonucleotides complementary to the coding regions of mRNA for arresting translation were published before the 1981 filing date of the priority application. For example, applicant relied upon the teachings of Salser (1978) to establish the recognition of different domains in mRNA and thus the fact that Miller failed to identify the coding regions as preferred targets was an important deficiency in the teaching of the prior art. Befort (1974) teaches that exogenous oligonucleotides used as antiviral agents do not enter the host cell nuclei. By suggesting that mRNA would not be available for as a target until it left the nucleus, Befort would be read by one of skill as limiting the time frame in which the target mRNA would be available for binding. This would provide yet another reason why one of skill would interpret the Miller text as merely suggesting that tRNA based arrest of protein expression is the most likely avenue of success for the arrest of protein expression. Finally, Pain and Clemens (1980) taught that proteins play a role in delivery of mRNA from the nucleus to the ribosomes. The declarants explain that one of skill would have considered these proteins as possible problems when attempting to target the mRNA coding regions for arresting protein expression.

Furthermore, and following the implications of the Pain and Clemens disclosure, the declarants cite to the presence of intracellular polyamines (spermine and spermidine) as other likely substances that would interfere with oligonucleotide binding. These ubiquitous, protein-like substances play a critical role in mRNA and rRNA structure and function. They would bind to the phosphate backbones of the nucleic acid of both the target mRNA and arresting oligonucleotide. According to

the declarants, nonspecific binding of polyamines potentially could have blocked the binding of the target mRNA and oligonucleotides under *in vivo* conditions.

The Examiner is obligated at a minimum to weigh the rebuttal references that predate the priority filing date of this applications and to revisit the question of obviousness with a fresh analysis. Moreover, according to the decisional law all the references offered for rebuttal should be considered with specificity and the reasons for maintaining rejection restated or withdrawn.

B. PATERSON AND HASTIE DO NOT ADDRESS THE KEY LIMITATIONS OF THE CLAIMED INVENTION.

The Examiner raises a second basis for maintaining the rejection. He urges that "nothing in the applicant's arguments negates the results reported in both of the secondary references (Paterson *et al.* and Hastie *et al.*)."

The Examiner notes that the title and abstract of Paterson "clearly disclose the fact that hybrid arrested translation occurs when cDNA is hybridized to mRNA *in vitro* and that Hastie shows that cDNA hybridized to mRNA prevents the translation of mRNA." The Examiner then states that these two references disclosing *in vitro* arrest of translation would lead one of skill to expect that "mRNA in vivo would behave the same way." Finally the Examiner concludes that knowing that mRNA could be arrested by oligonucleotides *in vivo*, it was a simple matter of routine titration to optimize the shortest sequence that permitted such inhibition.

Applicant agrees that *in vitro* inhibition of cell free translation by mRNA specific cDNA was known. However the applicant respectfully states that he has previously presented multiple, objective and persuasive reasons rebutting the conclusion of the Examiner that one of skill would view *in vitro* reports as suggesting that there was a "reasonable expectation" of successful *in vivo* inhibition. As evidence of the correctness of the applicant's position, applicant asks the Examiner to take note of the Paterson and Hastie references where they identify applications of their work. Paterson, on page 4373, states that there are numerous extensions of their work and list six applications. Hastie on page 1221

identified four applications. The Examiner is asked to take note of these applications. None of them suggests inhibiting *in vivo* protein expression.

The applicant specifically relies on the above recited seven reasons (see section 5) to explain why the *in vitro* results of Hastie and Paterson are not predictive of *in vivo* success. Among the reasons listed were differences between cell free translation conditions and living cells including osmotic potentials, salt and pH conditions are markedly different, the secondary structure of the mRNA *in vivo*, the potentially toxic effects upon a cell by the cation binding property of oligonucleotides, polyamines and transport proteins blocking binding, and the physical pressure and gel consistency of the cytosol.

In summary, the Examiner's statements regarding the failure of the applicant to negate the results of Hastie *et al.* and Paterson *et al.* are noted. But applicant sees no need to denigrate the work of Hastie and Paterson.

These two reports in combination with the other references simply do not give rise to an "expectation of success" needed to properly set forth the *prima facie* case of obviousness. If the Examiner does not withdraw this basis for rejection, he is respectfully asked to address the rebuttal arguments so that applicant can provide additional response and declaratory evidence specifically addressing his remaining concerns.

C. THE CROSSLINKING DESCRIBED BY SUMMERTON DOES NOT SUGGEST THE SPECIFIC LIMITATIONS OF THE PENDING CLAIMS.

Finally, the Examiner notes that "none of applicant's arguments are directed to the crosslinking of the oligonucleotide and the target sequence." Presumably the Examiner believes that irreversible crosslinking disclosed by Summerton would solve the problem of length and stability associated with the prior art use of trimers. Applicant notes that his invention differs from Summerton in two respects. First, the pending claims recite the use of oligonucleotides of a length suitable to bind to mRNA and arrest translation, and, second, the claims are limited to oligonucleotides that bind to the coding regions of mRNA. In contrast,

Summerton's teachings are limited to nucleic acid that crosslinks to viral nucleic acid targets.

Applicant urges that Summerton in combination with the other references does not suggest the use of oligonucleotides longer than Miller's trimers to avoid the need to irreversibly cross-link oligonucleotides when binding the oligonucleotides to the coding region of mRNA. Nor does the combination of references suggest the use of oligonucleotides shorter than the cDNA of Hastie and Paterson with crosslinking ability to arrest translation of specific mRNA. This is primarily because one of skill reading Summerton and the other three references would not believe that longer or cross-linking short oligonucleotides would be able to access the mRNA coding regions due to secondary structure. The various reasons are provided above and in the two attached Rule 132 declarations.

Having provided extensive argument and declarations in support of the objective facts underpinning the applicant's position and having addressed the three remaining concerns of the Examiner regarding obviousness, applicant now believes the obviousness rejection is rebutted by argument.

Applicant now believes the outstanding rejections have been fully addressed and overcome. Should the Examiner believe that prosecution can be expedited by a telephone interview, he is invited to call the undersigned attorney at the number provided below.

Respectfully submitted,

Kenneth A. Weber
Reg. No. 31,677

TOWNSEND and TOWNSEND KHOURIE and CREW
One Market Plaza
Steuart Street Tower, 20th Floor
San Francisco, California 94105

(415) 543-9600